

U.S.S.N. 09/534,717

2

Group Art Unit: 1647

In the claims:

Please amend the claims as follows:

**Claims 1-8. (Cancelled)**

9. (Previously presented) An isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a  $K_d$  of  $1 \times 10^{-10}$  M or less and a  $k_{off}$  rate constant of  $1 \times 10^{-3} \text{ s}^{-1}$  or less, as determined by surface plasmon resonance.

10. (Previously presented) The isolated human antibody of claim 9, or an antigen-binding portion thereof, which dissociates from human IL-12 with a  $k_{off}$  rate constant of  $1 \times 10^{-4} \text{ s}^{-1}$  or less.

11. (Previously presented) The isolated human antibody of claim 9, or an antigen-binding portion thereof, which dissociates from human IL-12 with a  $k_{off}$  rate constant of  $1 \times 10^{-5} \text{ s}^{-1}$  or less.

12. (Previously presented) The neutralizing antibody of claim 143, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an  $IC_{50}$  of  $1 \times 10^{-9}$  M or less.

13. (Previously presented) The neutralizing antibody of claim 143, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an  $IC_{50}$  of  $1 \times 10^{-10}$  M or less.

14. (Previously presented) The neutralizing antibody of claim 143, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an  $IC_{50}$  of  $1 \times 10^{-11}$  M or less.

**Claims 15-40. (Cancelled)**

U.S.S.N. 09/534,717

3

Group Art Unit: 1647

41. (Original) An isolated human antibody, or an antigen-binding portion thereof, which

- a) inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC<sub>50</sub> of 1 x 10<sup>-9</sup>M or less;
- b) has a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 25; and
- c) has a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 26.

42. (Original) The isolated human antibody, or an antigen-binding portion thereof, of claim 41 which further has a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 27; and a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 28.

43. (Original) The isolated human antibody, or an antigen-binding portion thereof, of claim 41 which further has a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 29; and a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 30.

44. (Original) An isolated human antibody, or an antigen-binding portion thereof, having a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 31, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 32.

45. (Original) The isolated human antibody of claim 44, comprising a heavy chain constant region selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgM, IgA and IgE constant regions.

46. (Original) The isolated human antibody of claim 45, wherein the antibody heavy chain constant region is IgG1.

47. (Original) The isolated human antibody of claim 44, which is a Fab fragment.

U.S.S.N. 09/534,717

4

Group Art Unit: 1647

48. (Original) The isolated human antibody of claim 44, which is a F(ab')<sub>2</sub> fragment.

49. (Original) The isolated human antibody of claim 44, which is a single chain Fv fragment.

Claims 50-87. (Cancelled)

88. (Currently amended) A pharmaceutical composition comprising the antibody or an antigen binding portion thereof, of claim 9, 41, 44, 151, 153, 164, 167, 168, 172, or 183, or 184, and a pharmaceutically acceptable carrier.

Claims 89-90 (Cancelled)

91. (Currently amended) The pharmaceutical composition of claim 89 88, wherein the further comprising an additional therapeutic agent, is selected from the group consisting of budenoside, ; corticosteroids, cyclosporin, sulfasalazine, aminosalicylates, 6-mercaptopurine, azathioprine, metronidazole, ; mesalamine, olsalazine, balsalazide, antioxidants, ; antibodies to IL-1 receptor, anti-IL-1 $\beta$  monoclonal antibodies, anti-IL-6 monoclonal antibodies, ; pyridinyl-imidazole compounds, anti-TNF antibodies, or fragments thereof, and anti-LT antibodies, anti IL-1 antibodies, anti IL-2 antibodies, anti IL-6 antibodies, anti IL-7 antibodies, anti IL-8 antibodies, anti IL-15 antibodies, anti IL-16 antibodies, anti IL-18 antibodies, anti SMAP II antibodies, anti GM-CSF antibodies, anti PGF antibodies, anti PDGF antibodies, anti CD2 antibodies, anti CD3 antibodies, anti CD4 antibodies, anti CD8 antibodies, anti CD25 antibodies, anti CD28 antibodies, anti CD30 antibodies, anti CD40 antibodies, anti CD45 antibodies, anti CD69 antibodies, anti CD80 (B7.1) antibodies, anti CD86 (B7.2) antibodies, anti CD90 antibodies, , methotrexate, FK506, rapamycin, mycophenolate mofetil, leflunomide, non-steroidal anti inflammatory drugs (NSAIDs), ibuprofen, corticosteroids, prednisolone, sulfasalazine, azathioprine, 6-mercaptopurines, , soluble p55 TNF receptor, soluble p75 TNF receptor, sIL-1RI, sIL-1RH, sIL-6R, sIL-13, antiinflammatory cytokines, IL-4, IL-10, IL-11, IL-13, and TGF $\beta$ .

Claims 92-141. (Cancelled)

142. (Previously presented) The isolated human antibody, or antigen-binding portion thereof, of claim 9, which is a recombinant antibody, or antigen-binding portion thereof.

143. (Previously presented) The isolated human antibody of any one of claims 9 to 11, wherein the antibody is a neutralizing antibody.

144. (Previously presented) The neutralizing antibody of claim 143, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* phytohemagglutinin blast proliferation assay (PHA assay) with an IC<sub>50</sub> of 1 × 10<sup>-7</sup> M or less.

145. (Previously presented) The neutralizing antibody of claim 143, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC<sub>50</sub> of 1 × 10<sup>-8</sup> M or less

146. (Previously presented) The neutralizing antibody of claim 143, or an antigen-binding portion thereof, which inhibits human IFNγ production with an IC<sub>50</sub> of 1 × 10<sup>-10</sup> M or less.

147. (Previously presented) The neutralizing antibody of claim 143, or an antigen-binding portion thereof, which inhibits human IFNγ production with an IC<sub>50</sub> of 1 × 10<sup>-11</sup> M or less.

148. (Previously presented) The neutralizing antibody of claim 143, or an antigen-binding portion thereof, which inhibits human IFNγ production with an IC<sub>50</sub> of 5 × 10<sup>-12</sup> M or less.

149. (Previously presented) The isolated human antibody, or antigen-binding portion thereof, of claim 41, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC<sub>50</sub> of 1 × 10<sup>-10</sup> M or less.

U.S.S.N. 09/534,717

6

Group Art Unit: 1647

150. (Previously presented) The isolated human antibody, or antigen-binding portion thereof, of claim 41, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC<sub>50</sub> of 1 × 10<sup>-11</sup> M or less.
151. (Previously presented) An isolated human antibody, or an antigen-binding portion thereof, which dissociates from human IL-12 with a K<sub>d</sub> of 1 × 10<sup>-10</sup> M or less and binds to an epitope on the p40 subunit of human IL-12.
152. (Previously presented) The isolated human antibody of claim 151, which neutralizes the activity of human IL-12.
153. (Previously presented) A neutralizing isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a k<sub>off</sub> rate constant of 1 × 10<sup>-3</sup> s<sup>-1</sup> or less, as determined by surface plasmon resonance.
154. (Previously presented) The neutralizing isolated human antibody of claim 153, or an antigen-binding portion thereof, which dissociates from human IL-12 with a k<sub>off</sub> rate constant of 1 × 10<sup>-4</sup> s<sup>-1</sup>.
155. (Previously presented) The neutralizing isolated human antibody of claim 153, or an antigen-binding portion thereof, which dissociates from human IL-12 with a k<sub>off</sub> rate constant of 1 × 10<sup>-5</sup> s<sup>-1</sup> or less.
156. (Previously presented) The neutralizing isolated human antibody of any one of claims 153 to 155, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC<sub>50</sub> of 1 × 10<sup>-7</sup> M or less.
157. (Previously presented) The neutralizing isolated human antibody of any one of claims 153 to 155, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC<sub>50</sub> of 1 × 10<sup>-8</sup> M or less.

U.S.S.N. 09/534,717

7

Group Art Unit: 1647

158. (Previously presented) The neutralizing isolated human antibody of any one of claims 153 to 155, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC<sub>50</sub> of 1 × 10<sup>-9</sup> M or less.

159. (Previously presented) The neutralizing isolated human antibody of any one of claims 153 to 155, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC<sub>50</sub> of 1 × 10<sup>-10</sup> M or less.

160. (Previously presented) The neutralizing isolated human antibody of any one of claims 153 to 155, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC<sub>50</sub> of 1 × 10<sup>-11</sup> M or less.

161. (Previously presented) The neutralizing isolated human antibody of any one of claims 153 to 155, or an antigen-binding portion thereof, which inhibits human IFN $\gamma$  production with an IC<sub>50</sub> of 1 × 10<sup>-10</sup> M or less.

162. (Previously presented) The neutralizing isolated human antibody of any one of claims 153 to 155, or an antigen-binding portion thereof, which inhibits human IFN $\gamma$  production with an IC<sub>50</sub> of 1 × 10<sup>-11</sup> M or less.

163. (Previously presented) The neutralizing isolated human antibody of any one of claims 153 to 155, or an antigen-binding portion thereof, which inhibits human IFN $\gamma$  production with an IC<sub>50</sub> of 5 × 10<sup>-12</sup> M or less.

164. (Previously presented) An isolated human antibody, or an antigen-binding portion thereof, which

- a) dissociates from human IL-12 with a k<sub>off</sub> rate constant of 1 × 10<sup>-3</sup> s<sup>-1</sup> or less, as determined by surface plasmon resonance;
- b) has a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 25; and
- c) has a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 26.

U.S.S.N. 09/534,717

8

Group Art Unit: 1647

165. (Previously presented) The isolated human antibody of claim 164, or an antigen-binding portion thereof, which dissociates from human IL-12 with a  $k_{off}$  rate constant of  $1 \times 10^{-4} s^{-1}$  or less.

166. (Previously presented) The isolated human antibody of claim 164, or an antigen-binding portion thereof, which dissociates from human IL-12 with a  $k_{off}$  rate constant of  $1 \times 10^{-5} s^{-1}$  or less.

167. (Previously presented) An isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and comprises:

a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 26; and

a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 25.

168. (Previously presented) An isolated human antibody, or an antigen-binding portion thereof, with a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 26, and with a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 25.

169. (Previously presented) The isolated human antibody, or an antigen-binding portion thereof, of claim 168, wherein the LCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 28 and the HCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 27.

170. (Previously presented) The isolated human antibody, or an antigen-binding portion thereof, of claim 169, wherein the LCVR further has CDR1 domain comprising the amino acid sequence of SEQ ID NO: 30 and the HCVR has a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 29.

171. (Previously presented) A pharmaceutical composition comprising an antibody or an antigen binding portion thereof, and a pharmaceutically acceptable carrier, wherein the antibody comprises:

a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 26; and  
a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 25.

172. (Previously presented) An isolated human antibody that binds human IL-12 and is the antibody J695, or an antigen binding portion thereof.

173. (Previously presented) A pharmaceutical composition comprising the isolated human antibody of claim 172 and a pharmaceutically acceptable carrier.

Claims 174-182. (Cancelled)

183. (Previously presented) An isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a  $K_d$  of  $1.34 \times 10^{-10}$  M or less, and neutralizes human IL-12.

184. (Previously presented) The isolated human antibody of claim 183, or an antigen-binding portion thereof, which dissociates from human IL-12 with a  $K_d$  of  $9.74 \times 10^{-11}$  M or less.

185. (Previously presented) The isolated human antibody, or antigen-binding portion thereof, of claims 183 or 184, which is a recombinant antibody, or antigen-binding portion thereof.

186. (Previously presented) The isolated human antibody of claim 185, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an  $IC_{50}$  of  $1 \times 10^{-7}$  M or less.

187. (Previously presented) The isolated human antibody of claim 185, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an  $IC_{50}$  of  $1 \times 10^{-8}$  M or less

U.S.S.N. 09/534,717

10

Group Art Unit: 1647

188. (Previously presented) The isolated human antibody of claim 185, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC<sub>50</sub> of 1 × 10<sup>-9</sup> M or less.

189. (Previously presented) The isolated human antibody of claim 185, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC<sub>50</sub> of 1 × 10<sup>-10</sup> M or less.

190. (Previously presented) The isolated human antibody of claim 185, or an antigen-binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC<sub>50</sub> of 1 × 10<sup>-11</sup> M or less.

191. (Previously presented) The isolated human antibody of claim 185, or an antigen-binding portion thereof, which inhibits human IFN $\gamma$  production with an IC<sub>50</sub> of 1 × 10<sup>-10</sup> M or less.

192. (Previously presented) The isolated human antibody of claim 185, or an antigen-binding portion thereof, which inhibits human IFN $\gamma$  production with an IC<sub>50</sub> of 1 × 10<sup>-11</sup> M or less.

193. (Previously presented) The isolated human antibody of claim 185, or an antigen-binding portion thereof, which inhibits human IFN $\gamma$  production with an IC<sub>50</sub> of 5 × 10<sup>-12</sup> M or less.

194. (Previously presented) The isolated human antibody of claim 185, or an antigen-binding portion thereof, which inhibits IL-12 binding to its receptor in an IL-12 receptor binding assay (RBA) with an IC<sub>50</sub> of 1 × 10<sup>-9</sup> M or less.

195. (Previously presented) The isolated human antibody of claim 185, or an antigen-binding portion thereof, which inhibits IL-12 binding to its receptor in an IL-12 receptor binding assay (RBA) with an IC<sub>50</sub> of 1 × 10<sup>-10</sup> M or less.

196. (Previously presented) The isolated human antibody of claim 185, or an antigen-binding portion thereof, which inhibits IL-12 binding to its receptor in an IL-12 receptor binding assay (RBA) with an IC<sub>50</sub> of 1 × 10<sup>-11</sup> M or less.

U.S.S.N. 09/534,717

11

Group Art Unit: 1647

197. (New) The pharmaceutical composition of claim 88, further comprising an additional therapeutic agent selected from the group consisting of anti- IL-1 antibodies, anti-IL-2 antibodies, anti- IL-6 antibodies, anti-IL-7 antibodies, anti-IL-8 antibodies, anti-IL-15 antibodies, anti- IL-16 antibodies, anti-IL-18 antibodies, anti- EMAP-II antibodies, anti-GM-CSF antibodies, anti-FGF antibodies, anti- PDGF antibodies, anti-CD2 antibodies, anti-CD3 antibodies, anti-CD4 antibodies, anti-CD8 antibodies, anti-CD25 antibodies, anti-CD28 antibodies, anti-CD30 antibodies, anti-CD40 antibodies, anti-CD45 antibodies, anti-CD69 antibodies, anti-CD80 (B7.1) antibodies, anti-CD86 (B7.2) antibodies, and anti-CD90 antibodies.

198. (New) The pharmaceutical composition of claim 88, further comprising an additional therapeutic agent selected from the group consisting of methotrexate, FK506, rapamycin, mycophenolate mofetil, leflunomide, non-steroidal anti-inflammatory drugs (NSAIDs), ibuprofen, prednisolone, 6-mercaptopurines, soluble p55 TNF receptor, soluble p75 TNF receptor, sIL-1RI, sIL-1RII, sIL-6R, sIL-13, antiinflammatory cytokines, IL-4, IL-10, IL-11, IL-13, TGF $\beta$ , Vx740, anti-P7s, p-selectin glycoprotein ligand (PSGL), p75TNFRlgG (Enbrel<sup>TM</sup>), p55TNFRlgG (Lenercept<sup>TM</sup>), pyridinyl-imidazole compounds, anti-gp39 antibodies, anti-CD40L antibodies, methotrexate, cytokine suppressive anti-inflammatory drugs (CSAIDs), leflunomide, MP, mesalazine, chloroquine/hydroxychloroquine, pencillamine, aurothiomalate, cochicine, salbutamol, terbutaline, salmeterol, theophylline, aminophylline, cromoglycate, nedocromil, ketotifen, ipratropium, and oxitropium.

199. (New) The pharmaceutical composition of claim 88, further comprising an additional therapeutic agent selected from the group consisting of anti-IRAK antibodies, anti-NIK antibodies, anti-IKK antibodies, anti-p38 antibodies, D2E7, cA2 (Remicade<sup>TM</sup>), CDP 571, 5-aminosalicylic acid, TNFR-Ig constructs, dexamethasone, aminosalicylic acid, IL-1ra, methylprednisolone, cyclophosphamide, methotrexate, 4-aminopyridine, tizanidine, interferon- $\beta$ 1a (Avonex<sup>TM</sup>), interferon- $\beta$ 1b (Betaseron<sup>TM</sup>), Copolymer 1 (Cop-1; Copaxone<sup>TM</sup>), hyperbaric oxygen, clabribine, anti- EMAP-II antibodies, IFN $\beta$ 1a, IFN $\beta$ 1b, and IL-1.

200. (New) A pharmaceutical composition comprising the antibody or an antigen binding portion thereof of claim 143, and a pharmaceutically acceptable carrier.

U.S.S.N. 09/534,717

12

Group Art Unit: 1647

201. (New) The pharmaceutical composition of claim 200, further comprising an additional therapeutic agent selected from the group consisting of budenoside, corticosteroids, cyclosporin, sulfasalazine, aminosalicylates, 6-mercaptopurine, azathioprine, metronidazole, mesalamine, olsalazine, balsalazide, antioxidants, antibodies to IL-1 receptor, anti-IL-1 $\beta$  monoclonal antibodies, anti-IL-6 monoclonal antibodies, pyridinyl-imidazole compounds, anti-TNF antibodies, or fragments thereof, and anti-LT antibodies.

202. (New) The pharmaceutical composition of claim 200, further comprising an additional therapeutic agent selected from the group consisting of anti- IL-1 antibodies, anti-IL-2 antibodies, anti- IL-6 antibodies, anti-IL-7 antibodies, anti-IL-8 antibodies, anti-IL-15 antibodies, anti- IL-16 antibodies, anti-IL-18 antibodies, anti- EMAP-II antibodies, anti-GM-CSF antibodies, anti-FGF antibodies, anti- PDGF antibodies, anti-CD2 antibodies, anti-CD3 antibodies, anti-CD4 antibodies, anti-CD8 antibodies, anti-CD25 antibodies, anti-CD28 antibodies, anti-CD30 antibodies, anti-CD40 antibodies, anti-CD45 antibodies, anti-CD69 antibodies, anti-CD80 (B7.1) antibodies, anti-CD86 (B7.2) antibodies, and anti-CD90 antibodies.

203. (New) The pharmaceutical composition of claim 200, further comprising an additional therapeutic agent selected from the group consisting of methotrexate, FK506, rapamycin, mycophenolate mofetil, leflunomide, non-steroidal anti-inflammatory drugs (NSAIDs), ibuprofen, prednisolone, 6-mercaptopurines, soluble p55 TNF receptor, soluble p75 TNF receptor, sIL-1RI, sIL-1RII, sIL-6R, sIL-13, antiinflammatory cytokines, IL-4, IL-10, IL-11, IL-13, TGF $\beta$ , Vx740, anti-P7s, p-selectin glycoprotein ligand (PSGL), p75TNFR IgG (Enbrel<sup>TM</sup>), p55TNFR IgG (Lenercept<sup>TM</sup>), pyridinyl-imidazole compounds, anti-gp39 antibodies, anti-CD40L antibodies, methotrexate, cytokine suppressive anti-inflammatory drugs (CSAIDs), leflunomide, MP, mesalazine, chloroquine/hydroxychloroquine, penicillamine, aurothiomalate, cochicine, salbutamol, terbutaline, salmeterol, theophylline, aminophylline, cromoglycate, nedocromil, ketotifen, ipratropium, and oxitropium.

204. (New) The pharmaceutical composition of claim 200, further comprising an additional therapeutic agent selected from the group consisting of anti-IRAK antibodies, anti-NIK antibodies, anti-IKK antibodies, anti-p38 antibodies, D2E7, cA2 (Remicade<sup>TM</sup>), CDP 571, 5-aminosalicylic acid, TNFR-Ig constructs, dexamethasone, aminosalicylic acid, IL-1ra, methylprednisolone, cyclophosphamide, methotrexate, 4-aminopyridine,

U.S.S.N. 09/534,717

13

Group Art Unit: 1647

tizanidine, interferon- $\beta$ 1a (Avonex<sup>TM</sup>), interferon- $\beta$ 1b (Betaseron<sup>TM</sup>), Copolymer 1 (Cop-1; Copaxone<sup>TM</sup>), hyperbaric oxygen, clabribine, anti- EMAP-II antibodies, IFN $\beta$ 1a, IFN $\beta$ 1b, and IL-1.

205. (New) The isolated human antibody of claim 9, or an antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a K<sub>d</sub> of 1.34 x 10<sup>-10</sup> M or less.

206. (New) The isolated human antibody of claim 9, or an antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a K<sub>d</sub> of 9.74 x 10<sup>-11</sup> M or less.